REMARKS

Claims 1, 2, 4-6, and 8-48 are pending in the application. The amendments to the claims find support in the specification and claims as filed. Support for the amendments to claim 1 may be found in the specification as filed, for example, at page 13, lines 4-31 (paragraphs 53, 54); page 25, lines 11-17 (paragraph 88); page 26, lines 11-20 (paragraph 91), and Example 3, page 70, line 5 to page 71, line 19 (paragraphs 263-267). Support for the amendment to claim 14 may be found in the specification, for example, at page 20, lines 25-30 and page 21, lines 1-2 (paragraph 76). Support for the amendment to claim 26 defining "R" may be found in the specification, for example, at page 7, lines 11-14 (paragraph 27). No new matter is added by way of the amendments.

Applicants thank the Examiner for her careful consideration of the present application and of cited references 1-35. However, Applicants note that the listings of references 36-94 presented in the Information Disclosure Statement mailed August 2, 2001 were not initialed to indicate their consideration by the Examiner. Applicants respectfully request the consideration of these references, and that the Examiner initial the IDS to indicate that these references have been considered. In the event that the Examiner considers these citations not to be in conformance, or that these references have not been considered for some other reason, Applicants respectfully request the Examiner to inform Applicants of the reasons therefore and means to present these references in a manner which would allow their consideration.

Claims 14 and 26 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4-6, 8-17, 20-33, and 38-41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of Hudziak (U.S. 5,725,856).

Claims 1, 2, 4-6, 8-33, 38-41 and 46-68 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of Carter (U.S. 6,054,297).

Claims 1, 2, 4-14, 20-33, and 38-41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of Bacus (U.S. 5,514,554).

Claims 1, 2, 8-14, 20-33, and 38-41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of Huston (U.S. 5,877,305).

Claims 1, 2, 8-14, 22-33, and 38-41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of King (U.S. 5,747,261).

Claims 1, 34, 37, 42, 44 and 45 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in combination with Hudziak (U.S. 5,725,856), Bacus (U.S. 5,514,554), Huston (U.S. 5,877,305) or King (U.S. 5,747,261) and further in view of Greene I (U.S. 5,824,311).

Claims 1 and 37 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of Greene II (U.S. 5,705,157).

Claims 1, 34-36 and 42-45 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in combination with Hudziak (U.S. 5,725,856), Bacus (U.S. 5,514,554), Huston (U.S. 5,877,305) or King (U.S. 5,747,261) in view of Greene I (U.S. 5,824,311) and further in view of Sliwkowski (J. Biol. Chem. **269**:14661-14665 (1994)) or Carter (U.S. 6,054,297).

Claims 1, 4-6, 8-19, 22-25, and 32 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Iwasa (5,217,713) in combination with Carter (U.S. 6,054,297), Hudziak (U.S. 5,725,856), Bacus (U.S. 5,514,554), Huston (U.S. 5,877,305) or King (U.S. 5,747,261).

Applicants respectfully traverse these rejections for at least the reasons indicated below.

The Rejections Under 35 U.S.C. § 112, second paragraph

Claims 14 and 26 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 as amended defines an antibody of the claim as a 4D5 monoclonal antibody such that the antibody shows a growth inhibitory effect on ErbB2 overexpressing cells in a manner that is dependent on the ErbB2 expression level and/or blocks binding of monoclonal antibody 4D5 to ErbB2. Claim 26 has been amended to state that R is capable of forming a

chemical bond with a linker. Accordingly, applicants believe that claims 14 and 26 particularly point out and distinctly claim the subject matter which applicant regards as the invention, and respectfully submit that the rejections to claims 14 and 26 under 35 U.S.C. § 112, second paragraph are overcome.

The Rejections to claims 1, 2, 4-6, 8-17, 20-33, and 38-41 under 35 U.S.C. § 103(a)

Claims 1, 2, 4-6, 8-17, 20-33, and 38-41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of Hudziak (U.S. 5,725,856). The Examiner cites Chari for discussing antibody conjugates comprising one or more maytansinoids, and cites Hudziak as discussing methods treating cancer comprising administering anti-ErbB2 antibodies conjugated to cytotoxic agents; that an anti-ErbB2 antibody is a growth inhibitory antibody; that Hudziak mentions the 4D5 monoclonal antibody; that the antibody may be an antibody fragment; and that Hudziak discusses specific linkers.

Applicants respectfully submit that claims 1, 2, 4-6, 8-17, 20-33, and 38-41 are not obvious under 35 U.S.C. § 103(a) over the cited references. The criteria needed to show that a claim is obvious under 35 U.S.C. § 103(a) have been detailed by the Federal Circuit:

"In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure." In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants have made the surprising discovery that tumors in animals that do NOT respond (or respond only poorly) to treatment with anti-ErbB2 antibodies DO respond when treated with such antibodies conjugated with maytansinoids. This result is surprising for at least the reason that such tumors would seem to be the ones least likely to respond based on their previous failure to respond to such antibodies.

Claim 1 is directed to a method for the treatment of a tumor in a mammal, and recites that the treatment includes a combination of steps, including "determining that said tumor is characterized by the overexpression of an ErbB2 receptor" and "determining that said tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody" as well as a step of "administering to the mammal a therapeutically effective amount of a conjugate of the anti-ErbB2 antibody with a maytansinoid." Claims 2, 4-6, 8-17, 20-33, and 38-41 depend from claim 1, and so each of claims 2, 4-6, 8-17, 20-33, and 38-41 includes these steps of claim 1 and also further elements.

However, neither Chari nor Hudziak discuss or suggest a treatment method directed to a tumor that overexpresses an ErbB2 receptor and does not respond, or responds poorly, to treatment with an anti-ErbB2 receptor; nor do the cited references suggest a method for treating a tumor in a mammal comprising performing together the steps of "determining that said tumor is characterized by the overexpression of an ErbB2 receptor" and "determining that said tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody" so that one can then administer "a therapeutically effective amount of a conjugate of the anti-ErbB2 antibody with a maytansinoid." Moreover, neither Chari nor Hudziak provide any motivation to combine such steps to provide a method of treating such tumors, nor to modify their teachings to provide a method comprising such a combination of steps. Lacking any such teaching or suggestion, the cited references, whether taken alone or taken together, further fail to provide any reasonable expectation of success for such a combination of steps.

Accordingly, since the cited references A) do not disclose a method for treating a mammalian tumor having a combination of steps including determining that the tumor is characterized by overexpression of an ErbB2 receptor and determining that the tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody; B) fail to provide any motivation to combine the cited references to provide these steps or to provide such a combination of steps; and C) fail to provide any reasonable expectation of success were the references to be so combined, applicants respectfully submit that claims 1, 2, 4-6, 8-17, 20-33, and 38-41 are not made obvious by Chari in view of Hudziak.

The Rejections to claims 1, 2, 4-6, 8-33, 38-41 and 46-48 under 35 U.S.C. § 103(a)

Claims 1, 2, 4-6, 8-33, 38-41 and 46-48 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of Carter (U.S. 6,054,297). Chari is presented for discussing the same topics cited the previous rejection. Carter is presented as discussing humanized 4D5 antibodies, including named species of such antibodies, and that humanized 4D5 antibodies may used as immunotoxins, where they are conjugated with a cytotoxic moiety. Carter is also cited as discussing that ErbB2 is amplified or overexpressed in many human malignancies.

The Examiner further states that the "claimed methods can be viewed as a methods drawn to administering a combination of ingredients known in the art to be useful for the same purpose," the Examiner then citing *In re Kerkhoven* for the proposition that "it is obvious to combine two compositions, in order to form a third composition, when each of the two compositions is taught by the prior art to be useful for the same purpose."

However, as discussed above, claim 1 and its dependent claims, including claims 2, 4-6, 8-33, 38-41 and 46-48, are method claims directed to a method of treating a tumor in a mammal including steps of determining that the tumor is characterized by overexpression of an ErbB2 receptor and of determining that the tumor does not respond, or responds poorly, to treatment with anti-ErbB2 antibody. The cited references do not provide such steps. The applicants' discovery that tumors in animals that do NOT respond (or respond only poorly) to treatment with anti-ErbB2 antibodies DO respond when treated with such antibodies conjugated with maytansinoids is surprising even in view of the cited references. The pending claims, being directed to such a method, and including such steps, are not directed to a composition comprised of a combination of two compositions to make a third composition as discussed in the citation to *In re Kerkhoven*. Moreover, even if *In re Kerkhoven* were *a propos* to the question of the claimed methods in the present application, the references cited by the Examiner fail to provide all the elements of the claimed invention, so that even were they to be combined, they fail to make the present methods obvious.

The Examiner cites Carter as teaching that ErbB2 is amplified or overexpressed in many human malignancies. In the section noted by the Examiner, Carter states "Furthermore, the extent of amplification is inversely correlated with the observed median patient survival time" suggesting that tumors having greater amplification of ErbB2 would be more resistant to

treatment, and thus suggesting that such treatment would be least successful in patients with the greatest amplification of ErbB2. Thus, Carter teaches away from directing such a treatment to tumors that are "characterized by the overexpression of an ErbB2 receptor" as required by the instant claims. Thus, not only does Carter fail to provide the missing elements of the instant claim, Carter teaches away from at least the element of step b) of claim 1. Accordingly, neither Carter nor Chari (as discussed previously) provide motivation or suggestion to provide the instant claims. Similarly, failing to provide all the elements of the claims, and failing to provide motivation or suggestion to provide the elements of the claims, and instead, teaching away from the present claims, neither Carter nor Chari, taken alone or taken together, provide any reasonable expectation of success for such a combination.

Accordingly, applicants respectfully submit that claims 1, 2, 4-6, 8-33, 38-41 and 46-48 are not made obvious by Chari in view of Carter.

The Rejections to claims 1, 2, 4-14, 20-33, and 38-41 under 35 U.S.C. § 103(a)

Claims 1, 2, 4-14, 20-33, and 38-41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of Bacus (U.S. 5,514,554). Chari is presented for discussing the same topics cited the previous rejection. Bacus is presented as discussing anti-ErbB2 antibodies that are growth inhibitory, induce cell death and apoptosis, that such antibodies may be conjugated to cytotoxic moieties, and that antibodies bind to a cancer antigen that is expressed or over expressed in certain cancer types.

However, Bacus fails to discuss methods of treating tumors in mammals including steps of determining that such tumors are characterized by overexpression of an ErbB2 receptor and determining that the tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Bacus fails in particular to discuss, suggest, or provide motivation to provide, a method including a combination of steps including the above-mentioned steps together with a step of administering a therapeutically effective amount of an anti-ErbB2 antibody conjugated with a maytansinoid. Similarly, failing to provide such a combination of steps, and failing to provide motivation or suggestion for such steps or such a combination of steps, Bacus fails to provide any reasonable expectation of success for such a combination.

As discussed above, Chari also fails to provide such elements, or to suggest or provide motivation to provide such a combination of steps, or to provide any reasonable expectation of success for such a combination. Chari taken together with Bacus also fails to provide any reasonable expectation of success for such a combination of steps. Thus, neither Bacus nor Chari provide all the elements of, nor provide motivation or suggestion to provide the instant claims.

Accordingly, applicants respectfully submit that claims 1, 2, 4-14, 20-33, and 38-41 are not made obvious by Chari in view of Bacus.

The Rejections to claims 1, 2, 8-14, 20-33, and 38-41 under 35 U.S.C. § 103(a)

Claims 1, 2, 8-14, 20-33, and 38-41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of Huston (U.S. 5,877,305). Chari is presented as above. Huston is presented by the Examiner as discussing a single-chain Fv comprising a binding site that binds to ErbB2, and as discussing methods of treating cancer comprising linking the single chain Fv to a therapeutic agent.

However, Huston does not discuss determining that a tumor is characterized by the overexpression of an ErbB2 receptor, nor does Huston discuss determining that a tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody, nor does Huston discuss a method of treatment including both these steps. Huston further fails to suggest or provide motivation to provide these steps, and provides no reasonable expectation of success for a treatment including such a combination of steps.

As discussed above, Chari also fails to provide such elements, or to suggest or provide motivation to provide such a combination of steps, or to provide any reasonable expectation of success for such a combination. Chari taken together with Huston also fails to provide any reasonable expectation of success for such a combination of steps. Thus, neither Huston nor Chari provide all the elements of, nor provide motivation or suggestion to provide the instant claims.

Accordingly, applicants respectfully submit that claims 1, 2, 8-14, 20-33, and 38-41 are not made obvious by Chari in view of Huston.

The Rejections to claims 1, 2, 8-14, 22-33, and 38-41 under 35 U.S.C. § 103(a)

Claims 1, 2, 8-14, 22-33, and 38-41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of King (U.S. 5,747,261). Chari is presented as above. King is presented by the Examiner as discussing methods for treating cancer that expresses high levels of ErbB2 by administering antibodies that bind ErbB2, the antibodies being liked to one or more toxic agents.

However, King does not discuss determining that a tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody, nor does King discuss a method of treatment including such a step. King further fails to suggest or provide motivation to provide a step of determining that a tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody, and provides no reasonable expectation of success for a treatment including such a step in a combination of steps. In fact, King cites a report correlating "gene amplification of this novel ErbB-related gene with a reduced disease-free survival in breast cancer patients," suggesting that treatment would be least effective in patients with the highest expression of the gene and so teaching away from the instant claims.

As discussed above, Chari also fails to provide such elements, or to suggest or provide motivation to provide such a combination of steps, or to provide any reasonable expectation of success for such a combination. Chari taken together with King also fails to provide any reasonable expectation of success for such a combination of steps. Thus, neither King nor Chari provide all the elements of, nor provide motivation or suggestion to provide the instant claims.

Accordingly, applicants respectfully submit that claims 1, 2, 8-14, 22-33, and 38-41 are not made obvious by Chari in view of King.

The Rejections to claims 1, 34, 37. 42. 44 and 45 under 35 U.S.C. § 103(a)

Claims 1, 34, 37, 42, 44 and 45 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in combination with Hudziak (U.S. 5,725,856), Bacus (U.S. 5,514,554), Huston (U.S. 5,877,305) or King (U.S. 5,747,261) and further in view of Greene I (U.S. 5,824,311). Chari, Hudziak, Bacus, Huston and King are cited by the Examiner as discussed above. Greene I is cited as discussing combinations of anti-ErbB2 (p185) antibodies that may have synergistic effect when used together. However, Greene I nowhere provides or suggests steps of determining that a tumor is characterized by the overexpression of an ErbB2

receptor, nor determining that a tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody, nor does Greene I alone or in combination with any or all of the other cited references provide any reasonable expectation of success for such a combination of steps.

As discussed above, failing to provide the individual steps of the instant claimed methods, and failing to provide such steps combined together to provide the instant claimed methods, and further failing to provide suggestion, motivation, or reasonable expectation of success, none of Chari, Hudziak, Bacus, Huston and King, taken alone or in combination, make claims 1, 2, 8-14, 22-33, and 38-41 obvious. Similarly, Greene I, alone and in combination with Chari, Hudziak, Bacus, Huston and King fails to provide the instant claimed methods, and fails to provide suggestion, motivation, or reasonable expectation of success for the instant claimed methods.

Accordingly, applicants respectfully submit that claims 1, 34, 37, 41, 44 and 45 are not made obvious by Greene I in view of Chari, Hudziak, Bacus, Huston and King.

The Rejections to claims 1 and 37 under 35 U.S.C. § 103(a)

Claims 1 and 37 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in view of Greene II (U.S. 5,705,157). Chari is cited by the Examiner as discussed above. Greene II is cited as discussing methods of using combinations of antibodies, which may be conjugated to an anticancer drug; that some tumors express ErbB2 and ErbB1 receptors; and methods of targeting both receptors to produce a synergistic effect. However, Greene II does not discuss or suggest a step of determining that a tumor characterized by overexpression of an ErbB2 receptor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Thus, neither Chari nor Greene II providing an element of claims 1 and 37, nor suggesting all the elements of these claims, nor a combination of steps including all these elements; nor providing any motivation to provide such steps or such a combination; nor providing any reasonable expectation of success for such a combination, applicants respectfully submit that claims 1 and 37 are not made obvious by Greene II in view of Chari.

The Rejections to claims 1, 34-36 and 42-45 under 35 U.S.C. § 103(a)

Claims 1, 34-36 and 42-45 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 5,208,020) in combination with Hudziak (U.S. 5,725,856), Bacus (U.S.

5,514,554), Huston (U.S. 5,877,305) or King (U.S. 5,747,261) in view of Greene I (U.S. 5,824,311) and further in view of Sliwkowski (J. Biol. Chem. **269**:14661-14665 (1994)) or Carter (U.S. 6,054,297).

Greene I, Chari, Hudziak, Bacus, Huston and King are discussed above. The Examiner cites Sliwkowski and Carter as making obvious a method comprising the use of a second anti-ErbB2 antibody: Sliwkowski is cited as discussing that antibody 2C4 may be used to inhibit the binding of heregulin to ErbB3; Carter is cited as discussing that huMab4D5 acts to recruit immune effector cells to a tumor.

As discussed above, none of Chari, Hudziak, Bacus, Huston, King, and Greene I taken alone or in combination, make claim 1 or its dependent claims obvious. For example, none of these references provide or suggest a method including together steps of determining that a tumor is characterized by overexpression of an ErbB2 receptor and of determining that a tumor characterized by overexpression of an ErbB2 receptor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody.

Applicants respectfully submit that neither Sliwkowski nor Carter provides or suggests such methods, or provides a reasonable expectation of success for such methods, nor do they do so even when taken together with the other cited references. The Sliwkowski and Carter references are discussed in more detail below.

Sliwkowski

Sliwkowski is cited by the Examiner as discussing that antibody 2C4 may be used to inhibit the binding of heregulin to ErbB3. The cited Sliwkowski reference suggests that, instead of requiring overexpression of ErbB2, breast cancer cells may require ErbB3 together with ErbB2. Claims 1, 34-36 and 42-45 of the instant application recite methods of treating tumors in a mammal including steps of determining that ErbB2 is amplified or overexpressed in a tumor, and of determining that a tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Sliwkowski, which does not discuss or suggest methods including such steps in combination, does not state or suggest all the elements of the instant claims,. In fact, Sliwkowski would tend to teach away from the elements of the instant claim by suggesting the need for ErbB3 receptors for ligand binding. Thus, Sliwkowski fails to provide all the elements of claims

1,34-36 and 42-45, does not suggest all the elements of these claims, nor does Sliwkoski, alone or in combination with the other cited references, provide any reasonable expectation of success for a combination of elements as required by the claims.

Accordingly, applicants respectfully submit that Sliwkowski in view of Chari, Hudziak, Bacus, Huston, King, and Greene I, taken alone or in combination, fail to make claims 1, 34-36 and 42-45 obvious.

Carter

Carter, as noted above, is cited by the Examiner as discussing humanized 4D5 antibodies, including named species of such antibodies, and that humanized 4D5 antibodies may used as immunotoxins, where they are conjugated with a cytotoxic moiety, and as discussing that ErbB2 is amplified or overexpressed in many human malignancies. Carter does not discuss determining that a tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. In addition, as discussed above, Carter teaches away from directing such a treatment to tumors that are "characterized by the overexpression of an ErbB2 receptor" as required by the instant claims. Thus, Carter fails to provide the missing elements of the instant claims, and also Carter teaches away from at least the element of step b) of claim 1. Carter thus provides no reasonable expectation of success for a method including all the elements of claim 1 and its dependent claims 34-36 and 42-45. Accordingly, applicants respectfully submit that Carter in view of Chari, Hudziak, Bacus, Huston, King, and Greene I, taken alone or in combination, fail to make claims 1, 34-36 and 42-45 obvious.

The Rejections to claims 1, 4-6, 8-19, 22-25, and 32 under 35 U.S.C. § 103(a)

Claims 1, 4-6, 8-19, 22-25, and 32 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Iwasa (5,217,713) in combination with Carter (U.S. 6,054,297), Hudziak (U.S. 5,725,856), Bacus (U.S. 5,514,554), Huston (U.S. 5,877,305) or King (U.S. 5,747,261).

Carter, Hudziak, Bacus, Huston and King are discussed above. Iwasa is cited by the Examiner as discussing an immunocomplex that comprises a bispecific antibody that binds to a tumor antigen and to a maytansinoid. The Examiner states "In view of the fact that the specification fails to provide a definition of the term "conjugate" and in interpreting the claims

broadly, the combination of Iwasa and any of Carter, Hudziak, Bacus, Huston or King may be used to make the claimed conjugates."

Applicants respectfully draw the Examiner's attention to page 55, lines 5-31 and page 56, lines 1-12 (paragraphs 196-199) which define anti-ErbB antibody-maytansionid conjugates and discuss their preparation. For example, "Anti-ErbB antibody-maytansinoid conjugates are prepared by chemically linking an anti-ErbB antibody to a maytansinoid molecule without significantly diminishing the biological activity of either the antibody or the maytansinoid molecule." (page 55, lines 6-8) Also, "There are many linking groups known in the art for making antibody-maytansinoid conjugates ... [including] disufide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups, or esterase labile groups..." (page 55, lines 15-19).

However, Iwasa fails to discuss or suggest methods for treating a tumor in a mammal including steps of determining that ErbB2 is amplified or overexpressed in a tumor, and of determining that a tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody, as required by claims 1, 4-6, 8-19, 22-25, and 32. Failing to discuss or suggest such methods, Iwasa also fails to provide any reasonable expectation of success for such methods. Accordingly, applicants respectfully submit that Iwasa in view of Carter, Hudziak, Bacus, or King, taken alone or in combination, fail to make claims 1, 4-6, 819, 22-25 and 32 obvious.

CONCLUSION

Applicants respectfully submit that claims 1, 2, 4-6, and 8-48 stand in allowable form, and respectfully request their reconsideration and allowance. Early notification of the allowance of all claims is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 referencing Attorney Docket No. 39766-0073 A2.

Respectfully submitted,

Dated: November 3, 2003

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